

Exercise, the diurnal cycle of cortisol and cognitive impairment in older adults

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ABSTRACT

Exercise has been shown to reduce the risk of developing Mild Cognitive Impairment and Alzheimer's disease as well as to improve cognition in healthy and cognitively impaired individuals. However, the mechanisms of these benefits are not well understood. The stress hypothesis suggests that the cognitive benefits attributed to exercise may partially be mediated by changes in the cortisol secretion pattern. Chronic stress may increase the risk of AD and exacerbate the cognitive deficits and brain pathology characteristic of the condition while physical activity has been shown to attenuate most of stress consequences and risk factors for AD. Initially, research on the effects of cortisol on cognition and physical activity focused on cortisol levels at one time point but the circadian pattern of cortisol secretion is complex and it is still unclear which aspects are most closely associated with cognitive function. Thus, the aim of this review was to analyze the exercise/stress/cognition hypothesis focusing on the effects of the diurnal cycle of cortisol on cognitive function and physical activity in older adults with and without cognitive impairment.

1. Introduction

Mild Cognitive Impairment (MCI) represents a higher level of cognitive deterioration than would be expected by aging but yet not meeting the criteria for a diagnosis of dementia (Petersen, 2009) and represents a 10–18% annual risk of converting to probable Alzheimer's Disease (AD) (Petersen, 2009; Risacher et al., 2009). There are several types of MCI, with the amnesic type (aMCI), in which memory loss is the predominant symptom, being more likely to progress to AD (Yaffe et al., 2006).

There are several risk factors for developing AD in addition to genetic factors (Corder et al., 1993). Prevalence increases with age (Querfurth and LaFerla, 2010), cardiovascular conditions (Helzner et al., 2009; Maher and Schubert, 2009; Strachan et al., 2008), oxidative stress (Querfurth and LaFerla, 2010), inflammatory markers (Parachikova et al., 2007), and chronic stress (Rothman and Mattson, 2010). An understanding of these risk factors for the development of counter-strategies to reduce deterioration from MCI to full-blown AD remains a key priority for improving individual and public health outcomes.

Observed links between chronic stress and deterioration of cognitive function provide a focus for investigation as the biological mechanisms linking stress and cognition are increasingly understood (de Quervain

et al., 2009; Dedovic et al., 2009; Lupien et al., 2007). The hypothalamic-pituitary-adrenal (HPA) axis is the major endocrine stress axis in humans. Cortisol, released in response to psychosocial and physical threat, affects metabolic, cardiovascular and central nervous systems both acutely and chronically. Basal cortisol secretion is regulated by the hypothalamic suprachiasmatic nucleus (SCN) in response to time of day and external zeitgebers such as light (Buijs and Kalsbeek, 2001). The fine-balanced regulation of stress-induced as well as basal cortisol secretion is essential for the maintenance of homeostasis and health and dysregulation is implicated in many of the risk factors for progression to AD (McEwen, 2000; Tortosa-Martínez and Clow, 2012a; Tsigos and Chrousos, 2002). In addition to exacerbation of these physical risk factors there is evidence of direct pathways linking dysregulation of cortisol secretion and cognitive impairment, which is reviewed here alongside evidence that participation in physical activity attenuates the negative impact of chronic stress and even normalizes cortisol dysregulation, accompanied by improvements in cognition.

Disruption of biological rhythms, including dysregulation of the circadian pattern of cortisol secretion, is associated with poor mental health and is suggested to causative acting via aberrant signaling to peripheral clock genes in the brain (Menet and Rosbash, 2011).

Physical and psychological stressors stimulate activity of the HPA axis which, over a prolonged period of time, can lead to changes in the

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circadian pattern of cortisol secretion, including reduced dynamic change over time and increased or decreased circulating basal levels. Excessive levels of cortisol over time produce an allostatic overload (McEwen, 2008) with severe health consequences including an increase in cardiovascular conditions (Björntorp, 1997; Nader et al., 2010; Rosmond et al., 1998), inflammation (McEwen, 2008), and oxidative stress (Pajović et al., 2006; Zafir and Banu, 2009); while decreasing levels of Brain Derived Neurotrophic factors (BDNF) (Duman and Monteggia, 2006), hippocampal volumes (Huang et al., 2009; Lupien et al., 1998) and cognitive function (Lucassen et al., 2014; Seeman et al., 1997), all considered risk factors for developing AD.

Thus, chronic stress may increase the risk of AD and exacerbate the cognitive deficits and brain pathology characteristic of the condition (Rothman and Mattson, 2010), including an increased formation of the two main hallmarks of AD, Amyloid β plaques and protein Tau “tangles” (Dong et al., 2008; Green et al., 2006; Jeong, 2006; Lee et al., 2009). Indeed, there is evidence showing that people exposed to chronic stress are 2.7 times more likely to develop AD and to experience more rapid disease progression (Wilson et al., 2006).

In parallel, regular physical activity has been shown to reduce the risk of developing MCI, dementia, and AD (Geda et al., 2010; Hamer and Chida, 2009). Exercise may also improve different cognitive domains, such as memory and executive function, in older adults with MCI (Cammisuli et al., 2017), dementia and AD (Groot et al., 2016). However, the mechanisms mediating these benefits remain unclear. One of the most recent theories, the stress hypothesis, suggests that the cognitive benefits associated with exercise could be mediated by changes in cortisol secretion (Tortosa-Martínez and Clow, 2012b).

Exercise has been shown to attenuate most of the consequences of chronic stress including AD risk factors, with evidence showing positive benefits of exercise for reducing cardiovascular conditions (Mora et al., 2007; Mueller, 2007), inflammation (Cotman et al., 2007), and oxidative stress (Radak et al., 2008); while increasing levels of Brain Derived Neurotrophic Factors (BDNF) (Kramer and Erickson, 2007) and hippocampal volume (Erickson et al., 2009, 2011).

Higher levels of physical activity and fitness seem to improve the ability for coping with stress (Puterman et al., 2011; Rimmele et al., 2007, 2009; Salmon, 2001) but there are some inconsistencies in the literature (Jackson and Dishman, 2006), and there is very limited evidence regarding the effects of exercise on stress in cognitively impaired populations.

Initially, research on the effects of cortisol on cognition and physical activity focused on cortisol levels at one time point (mostly morning levels). However, the circadian pattern of cortisol secretion is complex and it is still unclear which aspects are most closely associated with cognitive function: overall basal levels, indices of dynamic change or both. The cortisol secretory pattern in healthy participants follows a typical circadian rhythm across the day, sharply increasing within 30–45 min after awakening (the cortisol awakening response: CAR), and steadily declining during the remainder of the day, called the diurnal decline (DD) (Edwards et al., 2001).

Thus, in this narrative review we will analyze the exercise/stress/cognition hypothesis focusing on the effects of the diurnal cycle of cortisol on cognitive function and physical activity in older adults with and without cognitive impairment (see Fig. 1).

2. The diurnal cycle of cortisol and cognitive function

The evidence linking diurnal cortisol secretion levels with cognition in older adults remains mainly at a cross-sectional level (Table 1).

Abnormal cortisol secretory patterns include both overall basal levels such as high morning (Beluche et al., 2010; Geerlings et al., 2015) and evening levels (Geerlings et al., 2015); high daily average (Lee et al., 2007) and Area Under the Curve (AUC) (Lee et al., 2007; Ouanes et al., 2017); and flattening of the cortisol diurnal pattern (Beluche et al., 2010; Evans et al., 2011; Kovach et al., 2011) have been

associated with worse cognitive performance in healthy older adults.

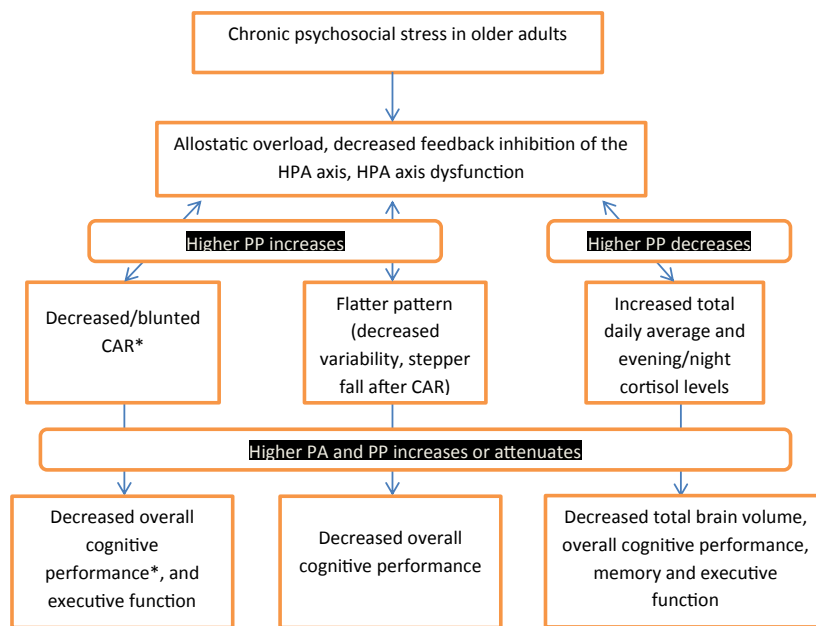
Although the role of the CAR in cognitive performance remains controversial emerging evidence from carefully controlled studies suggests that larger CARs are associated with better executive function, both between and within individuals. Some studies suggest that a higher CAR indicates better overall cognition (Evans et al., 2011) or executive function (Evans et al., 2012) in healthy older adults. This is in line with the idea that the CAR is an adaptive response, increasing in anticipation of daily activities at awakening (Adam et al., 2006; Stalder et al., 2010). The magnitude of the CAR may decrease when impaired prospective recall precludes this anticipatory response and it seems to predict progression from healthy aging to MCI, although not to dementia (Peavy et al., 2012). Similarly, Oosterholt et al. (2015) showed that in clinical burnout an attenuated CAR was associated with poorer performance on the updating component of the ‘3-back’ task, and an increased frequency of cognitive failures although a similar relationship was not shown in healthy adults (Ennis et al., 2016). However, in a 50 day case-study of a healthy young male, days with a greater CAR predicted better same morning executive function (Law et al., 2015). This finding is again consistent with the marked state variation in the CAR and the proposal that the CAR prepares one for the day ahead (Law et al., 2013). A similar state relationship between same day larger CARs and plasticity of the motor cortex has also been demonstrated (Clow et al., 2014).

The CAR is reported to be related with some hippocampal functions such as long term memory and spatial orientation (Wolf et al., 2005) with no CAR observed in individuals with unilateral and bilateral hippocampal lesions (Buchanan et al., 2004), nor in those with severe global amnesia (Wolf et al., 2005). A larger CAR has also been associated with increased hippocampal volume in healthy young men (Pruessner et al., 2007). In an experimental manipulation, Rimmele et al. (2010) demonstrated that pharmacologic suppression of the CAR using metyrapone (a cortisol synthesis inhibitor) impaired memory for prior-day learnt text and imagery in a free recall task. In a sample of elderly participants without dementia, Geerlings et al. (2015) linked higher levels of cortisol at 45-min post-awakening with better processing speed and executive functioning, and slightly increased white matter. The results implicate a possible role of the CAR due to the timing of the cortisol assessment.

However, other studies have found an inverse correlation between the CAR and declarative and verbal memory (Almela et al., 2012; Hidalgo et al., 2016). Interestingly enough (Almela et al., 2012), found that the CAR was positively associated with working memory but only in men. This research group suggested that the CAR might be related differently to cognitive domains dependent on the hippocampus (i.e., declarative memory), than to those that are more dependent on pre-frontal cortex functioning such as executive functioning (i.e., working memory). It is also possible that there is an inverted U-shaped relationship between the CAR and cognition (Moriarty et al., 2014), which might partially explain the discrepancies found in the literature.

There are only two studies examining the relationship between the diurnal cycle of cortisol and cognition in people with cognitive impairment. Wolf et al. (2002) found, with a sample of young, healthy older adults and people diagnosed with MCI, that a high average of cortisol levels indicated a worse performance in the paragraph recall, but only in those with MCI. This study did not include a CAR measurement and the first morning sample was collected at 9:00 without controlling for waking time. Also the cognitive assessment was performed within three months of the day of the salivary collection, which could bias the results in the case of people with MCI.

On the opposite side, Peavy et al. (2009) found that high average of cortisol levels were associated with a decrease rate of cognitive decline in subjects with MCI and not in healthy older adults. This is a surprising result, although it is possible that the method of measurement had an influence on the results. The researchers calculated the cortisol average based on five samples taken over the course of one day, including



*It should be noted that there are conflicting results in regards to the effects of stress on the CAR and the role of the CAR on cognition

PP=Physical performance; PA=Physical activity

Fig. 1. Consequences of chronic stress on cognition in older adults and the possible mediating role of physical activity.

awakening and 30 min after awakening. High CAR levels could influence the total cortisol average leading to misinterpretation of the results.

In summary, although the exact relationship between cognitive function and the diurnal cycle of cortisol is not yet clarified, current evidence seems to indicate that a more dynamic cortisol secretion pattern, as opposed to a flatter profile, represents a healthier profile and a better adaption response to cognitive decline. A parallel could be established here with Heart Rate Variability (Evans et al., 2011), a dynamic autonomic measure closely related to stress, in which a higher variability is indicative of better cardiovascular health (Thayer et al., 2010) and better cognitive functioning (Thayer et al., 2009).

3. Exercise and the diurnal cycle of cortisol

Studies conducted with healthy older adults have shown a positive relationship between a more dynamic cortisol secretion pattern and physical performance but not physical activity levels (Table 2).

Physical performance was measured by different tests such as the six minute walk test and the Rockport test to assess cardiovascular performance, chair rises for lower body strength, grip strength, the timed get up and go test for dynamic balance and agility, the flamingo test for balance, and walking speed tests for assessing gait. One study (Sousa et al., 2017) used the Short Performance Battery (Guralnik et al., 1994), which combines the results of gait speed, chair stand and balance tests. Better performance in these tests are indicative of better overall health and physical functioning.

Higher morning, evening and night-time cortisol levels have been associated with lower walking speed and balance (Gardner et al., 2011; Gardner et al., 2013a; b), as well as worse cardiovascular (Lucertini et al., 2015) and overall physical performance (Sousa et al., 2017). Similarly, higher diurnal levels and AUC have been associated with lower walking speed and worse cardiovascular performance (Kumari et al., 2010; Lucertini et al., 2015). A lower diurnal cortisol drop and a flatter pattern, indicate lower walking speed (Gardner et al., 2011;

Gardner et al., 2013a; b; Kumari et al., 2010) and higher lower body strength (Gardner et al., 2013a; b). In the three studies analyzing the relationship between the CAR and physical performance, a higher magnitude of the CAR indicated faster walking speed (Gardner et al., 2013a; b; Kumari et al., 2010; Pulpulos et al., 2016).

High levels of physical activity and physical performance have been shown to produce positive effects on brain plasticity and regional gray matter volume, especially in the hippocampus and the prefrontal areas (Erickson et al., 2013). This is of relevance not only because these areas are responsible for relevant cognitive functions, such as memory and executive function, but also because they are associated with the control of the cortisol feedback inhibition mechanism (McEwen and Morrison, 2013). Thus, it is plausible that exercise yields converging benefits in cognition and the cortisol secretion pattern (Lucertini et al., 2015). However, most evidence is based on cross-sectional studies and with healthy older adults. There are very few studies analysing the effects of exercise on the diurnal cortisol secretion pattern and cognitive function with a cognitively impaired sample, and none of them includes participants with Alzheimer's disease. To the best of our knowledge, there are only three published studies in this regard, one cross-sectional (Dijckmans et al., 2017) and two exercise interventions (Baker and Frank, 2010; Tortosa-Martínez et al., 2015), which include a sample of older adults with aMCI.

4. The influence of exercise on cognition through changes in the diurnal cycle of cortisol

At a cross-sectional level, Dijckmans et al. (2017) showed that a greater variance in cortisol levels across the day from morning to evening was associated with better physical performance and overall cognition in a sample of healthy older adults (N = 30) and people with MCI (N = 30). No relationship was found between the CAR and cognition or physical performance. Walking speed and the Six Minute Walk Test (6MWT) were significantly correlated with both cognition and cortisol levels, indicating a link between the three variables, although

Table 1
Cross-sectional studies analyzing the relationship between the diurnal cycle of cortisol and cognition in older adults.

Authors	Sample	Cortisol measurement	Cognitive measurement	Results
Almela et al., 2012	N = 88 (Men: 63.41 ± 4.91; Women: 63.73 ± 3.90)	Waking, 30', 45' and 60' after waking (two consecutive days)	Logical Memory and Auditory Verbal Learning Test; Spatial Span and Spatial Working Memory	↑ CAR ↓ declarative memory in men and women ↑ CAR ↑ working memory performance only in men
Beluche et al., 2010	N = Men 111 (72.9 ± 4.4); Women 86 (72.8 ± 4.7)	Before cognitive testing (8h40 ± 20'), 15h40 ± 40', and 21h40 ± 35' (replicating the times in a quiet day)	Isaacs Set Test; Benton's visual retention test; Trail Making Test B, MMSE	At baseline and in longitudinal analysis, ↑ morning cortisol and a flatter slope were associated with ↓ cognitive performance.
Ennis et al., 2016	N = 56 M = 53.04, SD = 16.94 young (N = 17), middle-aged (N = 21), and older adults (N = 18) N = 50 (73.9 ± 6.9)	Waking, 30' later, and then approximately every three hours until 9:17 p.m. on average during 10 consecutive days Waking, 15', 30' and 45'; 3hr, 6hr, 9hr, 12hr after waking (two consecutive days)	Episodic memory (yes-no associative recognition task); Working memory (3-back and Reading Span); Processing speed (Letter Comparison and Pattern Comparison) National Adult Reading Test; the Hopkins Verbal Learning Test (HVLIT); Verbal and Semantic Fluency Tests, and Trail-Making Test A and B	A more positive CAR slope was related to better episodic memory regardless of age ↑ waking cortisol ↑ working memory ↑ CAR and steeper fall thereafter were associated with ↑ overall cognitive performance
Evans et al., 2012	N = 50 (73.9 ± 6.9)	Waking, 15', 30' and 45' (two consecutive days)	Hopkins Verbal Learning Test (HVLIT), and Trail-Making Test A and B	Earlier peak and ↑ CAR were associated with ↑ executive function
Geerlings et al., 2015	N = 4244 (76 ± 5)	The evening before the clinic visit, prior to going to sleep and in the morning 45' after waking	(1) memory composite score (modified version of the California Verbal Learning Test); (2) processing speed composite score, (Stroop 1 and 2, the DSST, and the Figure Comparison Test); (3) executive function composite score, (Cambridge Neuropsychological Test Automated Battery Spatial Working Memory test (short version), the Digits Backward test, and Stroop 3)	↑ evening cortisol was associated with ↓ total brain volume and cognitive performance ↑ levels of morning cortisol were associated with slightly ↑ normal white matter volume and ↑ processing speed and executive functioning, but not with gray matter volume or with memory performance.
Hidalgo et al., 2016	N = 64 (32 men, 64.4 ± 4.2; 32 women (on two consecutive days)	Waking; 30' and 45' post-wake; 12am, 4pm, 8pm, and bedtime (two consecutive days)	Logical Memory and Verbal Paired Associates tests Family Pictures test Letter Number Sequencing (LNS) and Digit Span (DS), Spatial Span (SS)	↑ CAR ↓ verbal (significantly) and visual (marginally) memory performance. No associations with working memory.
Kovach et al., 2011	N = 111 (87 ± 7) older adults with dementia	30' after waking, 45' after breakfast, and 45' minutes before and after dinner	MMSE and the Cumulative Illness Rating Scale -Geriatric (CIRS-G)	Flatter pattern was associated with ↓ MMSE ↑ Afternoon increase ↑ Illness burden However, these trends did not reach statistical significance.
Lee et al., 2007	642 women 325 men (61.1 ± 6.0)	Before, during, and after cognitive testing as well as at visit completion	Language, processing speed, eye-hand coordination, executive functioning, verbal memory and learning, visual memory, and visuoconstruction	↑ levels of mean cortisol and AUC were associated with ↓ in all cognitive domains but visuoconstruction
Ouanes et al., 2017	N = 643 (71.5 ± 4.5)	Waking, 30' after waking, at 11 a.m. and at 8 p.m.	MMSE; Grober and Buschke Double Memory Test (DMT); DO40 picture naming test, the letter (phonemic) and the category (semantic) fluency tasks; Stroop Test; Consortium to Establish a Registry for Alzheimer's Disease (CERAD); Clinical Dementia Rating (CDR) scale	↑ AUC ↑ CDR (indicating worse cognitive performance) ↑ AUC ↓ MMSE
Peavy et al., 2009	N = 61 healthy older adults (78.5 ± 6.4) 41 with MCI (79.2 ± 5.2). 52 were followed longitudinally (78.6 ± 5.4)	Waking; 30' post-wake; 2pm, 4pm, and bedtime	Mattis Dementia Rating Scale Immediate and delayed recall from Wechsler Memory Scale—Revised List learning and retention from the California Verbal Learning Test Verbal and visual material from the Dementia Rating Scale memory subscale.	↑ cortisol levels were associated with ↓ cognitive decline only in subjects with MCI
Wolff et al., 2002	N = 14 young (27.0 ± 2.1); 28 healthy older adults (68.6 ± 1.2); 16 with MCI (70.9 ± 2.0)	9 am, 11 am, 2 pm, 4 pm, 9 pm, and 11 pm	GDS, MMSE, Wechsler Memory Scale Revised (paired associates and digit span) and the Guild Memory test (paragraph recall)	↑ average cortisol levels were associated with ↓ immediate paragraph recall only for people with MCI

Table 2
The influence of physical performance and physical activity levels on the diurnal cycle of cortisol in older adults.

Authors	Sample	Cortisol measurement	Physical activity measurement	Results
Gardner et al., 2011	N = 1143 (73.4 ± 4.17)	Phase 5. Waking, 30' post-wake, 2pm, 10pm (on two consecutive days)	Get up and go test and Flamingo test	↑ Night-time cortisol levels ↓ Walking speed ↓ Balance ↑ Diurnal drop ↑ Walking speed
Gardner et al., 2013a, b	6 cohort studies: Boyd Orr; Caerphilly Prospective Study (CaPS); Hertfordshire Cohort Study (HCS); MRC National Survey of Health and Development (NSHD); Longitudinal Ageing Study Amsterdam (LASA); and the Whitehall II (WHII) study Ages: between 50 and 92 N = 36, 18 men, 18 women (70.7 ± 5.66)	Different protocols including morning levels, CAR, and rest of the day	Walking speed; Chair rises; standing balance; grip strength	↑ morning cortisol, ↓ diurnal drop, ↑ CAR, ↓ night time cortisol were associated with ↑ walking speed ↑ Diurnal drop ↑ Chair rises ↑ Night time cortisol ↓ balance No associations with grip strength
Heaney et al., 2014	N = 36, 18 men, 18 women (70.7 ± 5.66)	Awakening: 30' post-waking; 3hr, 6hr, 9hr, and 12hr after waking	Physical activity scale from the West of Scotland Twenty-07 Study	No differences in cortisol measurements but ↓ levels of cortisol:DHEA ratio for those who engaged in 1hr per week of physical activity but only in the high stress group
Kumari et al., 2010	N = 2802 (60.9 ± 5.9)	Waking, 30' post-waking; 2.5hr, 8hr, and 12hr after waking; and bedtime	Walking speed over 8 feet course	Those with a ↓ CAR, ↑ diurnal cortisol and flatter pattern showed ↓ walking speed
Lucertini et al., 2015	N = 22 men 68.13 ± 1.28	30' post-awake, 12.00, 15.00, 18.00, 21.00, 24.00 h	Rockport Walking test	↓ basal cortisol, especially in the evening and midnight, and ↓ area-under-the-curve for total daily cortisol levels in High Fit individuals
Pulopulos et al., 2016	N = 86 (64.92 ± 3.93)	Waking: 30' post-awake; 45' post-wake	Walking speed: 10 m at usual speed and as fast as possible	↑ CAR ↑ Walking speed
Strahler et al., 2010	N = 26 young adults (24.6 ± 2.0), 33 older adults (62.2 ± 6.7), 27 younger ballroom dancers (21.1 ± 4.4) and 31 older ballroom dancers (60.2 ± 6.8)	Waking: 30' post-wake; 11am, 3pm, 8pm	To be included, dancers had to dance at least twice per week and compete one a month	↑ basal salivary α-amylase ↓ amount of physical activity and aging but no effects for cortisol measurements.
Sousa et al., 2017	Kingston (N = 81; 69.0 ± 2.4) Saint-Hyacinthe (N = 81; 68.3 ± 2.5) Tirana (N = 57; 69.4 ± 3.4) Manizates (N = 90; 68.9 ± 2.7)	Waking, 30' and 60' post-waking; 3pm, and bedtime	Short Physical Performance Battery	↓ cortisol peak (30' post-waking), ↑ cortisol bedtime, and ↓ ratio between these two indices indicated ↓ physical performance

this relationship did not reach statistical significance.

Baker and Frank (2010) showed that a three-month high intensity aerobic exercise program improved executive function in older adults with amnesic MCI, which was more pronounced for women than for men. Furthermore, within the exercise group, cortisol levels decreased in women while increased in men. However, this study used a one time-point cortisol measure (ranging from 8:00 to 10:00), without controlling for time of awakening. Considering the circadian pattern of cortisol, this might not be the most accurate measure.

Tortosa-Martínez et al. (2015) analyzed the effects of a three-month moderate intensity aerobic exercise program in older adults with amnesic MCI on cognition and the diurnal cycle of cortisol secretion. In this study, at baseline, better physical performance, as measured with the 6MWT and the Timed get up and go test (TGUG) was associated with a higher peak of cortisol at 30 min and a subsequent drop from this peak at noon. Also better performance in the 6MWT was associated with lower cortisol values at 21:00. No correlations were found with the AUC or the CAR. These data would again indicate that more dynamic cortisol secretion pattern would be indicative of better physical performance.

After the intervention, there was a significant increase in the drop between the peak of cortisol at 30 min after awakening and the subsequent drop from this peak to noon in the exercise group. The exercise group also showed a tendency for an increased peak of cortisol at 30 min ($p = 0.068$) and of the magnitude of the CAR ($p = 0.069$). Thus, almost the same aspects of the diurnal cortisol profile found to be related to fitness at baseline were improved with aerobic exercise. An unexpected result was that total cortisol values as measured by the total mean or the AUC were not significantly changed with exercise.

At the same time, the exercise group improved executive function performance, while memory remained unchanged. Other studies have found positive changes in memory in people with MCI after six months of exercise training (Lautenschlager et al., 2008; Nagamatsu et al., 2013). Thus, it is possible that longer periods of training could result on memory improvements and different changes in the cortisol secretion pattern, such as total lower levels of diurnal cortisol.

5. Conclusion, limitations and future research

The available evidence supports the stress hypothesis, implicating that the cognitive benefits associated with exercise could be at least partially mediated by changes in the diurnal cortisol secretion pattern to a more dynamic profile. These benefits are probably mediated by the effects of exercise on the hippocampus and the prefrontal cortex, both implicated on cognition and the regulation of the diurnal pattern of cortisol. However, most studies included healthy older adults and have analyzed this phenomenon partially, focusing either on the effects of physical activity on cortisol or the effects of the diurnal cycle of cortisol on cognition, but not all variables at the same time. Furthermore, there are limitations on methodological factors for assessing cortisol patterns, and especially the CAR, that should be noted. For example, obtaining samples from at least two consecutive days and if possible six days is highly recommended. Similarly, objective control of the sampling time accuracy and adherence as well as adequate participant instructions and sampling protocols are also relevant. Also a minimum of three sampling points are needed for assessing the CAR: on awakening, 30 min and 45 min (Stalder et al., 2015). Many of the studies analyzed in this review fail to meet this guidelines.

Thus, more research is needed to test the stress hypothesis including randomized controlled trials analyzing the effects of exercise on the diurnal cortisol secretion pattern and cognition, with cognitively impaired participants (aMCI and AD) and using carefully controlled protocols of cortisol sampling. It would also be of high interest adding measures of the effect of exercise on the hippocampus and the prefrontal cortex.

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